rder. Br. J. med. Psychol.,

D. C. & COLE, P.V. (1976).
r cigarette smoking and
J. J., 1, 1043–1046.
PATEL, U.A., COLE, P.V. &
Comparison of effect on
rbon monoxide absorption
icotine cigarettes. Br. med.

. B., KOZLOWSKI, L.T.,
. & LIEBLING, B. (1977).
of psychological and
s of smoking. J. exp.

T., FINK, R. & JARVIK.
ette smoking with nicotine
ogia, 28, 247–259.
.W. & BALL, K.P. (1974).
low-tar and low-nicotine

9). Quantitative electro-
and smoking deprivation.

(1968). Relationship of
to 'tar' rating. National
graphs, 28, 29–33.

Br. J. clin. Pharmac. (1978), 5, 293–297

EFFECT OF URINARY pH AND NICOTINE EXCRETION RATE ON PLASMA NICOTINE DURING CIGARETTE SMOKING AND CHEWING NICOTINE GUM

C. FEYERABEND & [1]M.A.H. RUSSELL

Poisons Unit, New Cross Hospital, London SE14 and
[1]Addiction Research Unit, Institute of Psychiatry, Maudsley Hospital, London SE5

1 Plasma nicotine levels produced by chewing nicotine gum were compared with those obtained by cigarette smoking under conditions of controlled urinary pH.

2 Although absorption was slower, plasma levels comparable to cigarette smoking were built up on 4 mg (but not 2 mg) nicotine gum.

3 Urinary excretion of nicotine was influenced markedly by pH and the rate of urine flow.

4 Plasma nicotine was higher under alkaline compared to acidic conditions ($P < 0.001$) but the rate of urinary nicotine excretion appeared to have little effect on the plasma level.

Introduction

Since the urge to smoke may be related to a need for nicotine, alternative methods of administering the drug, either in aerosols or chewing-gum, have been proposed (Fernö, Lichtneckert & Lundgren, 1973; Herxheimer, Griffiths, Hamilton & Wakefield, 1967). During an investigation of the plasma concentrations produced by nicotine chewing-gum (Russell, Feyerabend & Cole, 1976) urinary pH was controlled in order to standardise the rate of urinary nicotine excretion, since this has been shown to be pH dependent (Beckett, Rowland & Triggs, 1965; Beckett & Triggs, 1966; Haag & Larson, 1942). We also measured the urinary excretion of nicotine and found that besides being pH dependent it was, under acidic conditions, proportional to urine flow. This is contrary to previous reports (Beckett, Gorrod & Jenner, 1971a; Beckett, Gorrod & Jenner, 1971b; Beckett, Gorrod & Jenner, 1972).

Methods

Chewing-gum containing either 2 or 4 mg of nicotine, buffered at an alkaline pH, was supplied by A.B. Leo, Helsingborg, Sweden (Fernö *et al.*, 1973). The test cigarette was a brand with a nicotine yield of 1.3 mg. A single volunteer was used. He was a healthy male smoker, aged 38 years, who regularly smoked just over 20 cigarettes per day and inhaled deeply. Before each day's experiment he refrained from smoking for at least 12 h. The urine was acidified by administering 2 g doses of ammonium chloride in gelatine capsules at 23.00 h on the day before and 07.00, 10.00 and 15.00 h on the day of an experiment. The same dosage of sodium bicarbonate in gelatine capsules was used to maintain the urine alkaline. Fluid intake was not controlled. During each experiment the subject was ambulant, took fluids as usual, and had lunch between 13 h 30 min and 13 h 50 min.

Plasma and urine nicotine levels were studied on six separate days when the subject was either smoking or taking 2 mg or 4 mg nicotine chewing-gum, each under both acidic and alkaline control of urinary pH. On smoking days, one cigarette was smoked to about 3 mm from the tip over 5 min once an hour for 8 h. When taking nicotine chewing-gum, one piece was chewed for 30 min every hour for 8 h. The dose of nicotine administered over 8 h was 10.4, 16.0 and 34.0 mg respectively for the cigarettes, 2 mg and 4 mg gum. About 91% of the nicotine in the gum is released during 30 min chewing (Fernö *et al.*, 1973) and more than 90% of nicotine in mainstream smoke is retained after inhalation (Armitage, Dollery, George, Houseman, Lewis & Turner, 1975). The bladder was emptied at 07.00 h. Urine samples were then collected every hour just before a cigarette or gum was taken, starting at 09.00 h. The volume and pH of the urine were measured immediately and aliquots stored at −20°C.

Blood samples (5 ml) were obtained from a forearm vein via an indwelling cannula. The plasma was separated within 3 h and stored at −20°C. Blood was taken hourly just before starting each cigarette or gum on six different experimental days. This frequency of

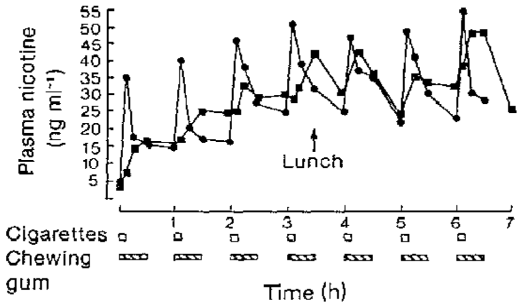


Figure 1 Plasma nicotine levels under conditions of controlled acidic urinary pH when (●) smoking one cigarette and (■) chewing one 4 mg nicotine gum every hour for 7 h.

sampling did not allow comparison of peak plasma levels. On two further days, to compare the rates of absorption of nicotine from cigarettes and the 4 mg gum, more frequent samples were taken at 7, 15, 30 and 60 min after starting each hourly gum or cigarette (Figure 1).

Nicotine in plasma and urine was analysed by gas-liquid chromatography (Feyerabend, Levitt & Russell, 1975).

Results

Nicotine absorption was much slower from the chewing-gum than from cigarette smoking, 15–30 min being required to reach peak values compared with less than 2 min after a cigarette (Figure 1). The average ±s.d. increase in plasma nicotine after each piece of gum (4 mg nicotine) was only 11.9 ± 2.4 ng ml^{-1} compared with 27.8 ± 4.6 ng ml^{-1} after each cigarette (1.3 mg nicotine).

Plasma nicotine concentrations similar to those from smoking were built up on the 4 mg gum, but on 2 mg gum they were lower. Taking the areas under the curves in Figure 2, with those produced by smoking as representing 100%, the plasma nicotine concentration from the chewing-gum was 60% and 114% for the 2 mg and 4 mg gum respectively under acidic conditions; 77% and 118% when the urine was alkaline. When the peak levels are included (Figure 1) the area under the curve for the 4 mg gum is 91% of that produced by cigarettes. The subject reported no desire to smoke while on the 4 mg gum but was not satisfied by the 2 mg gum.

Plasma nicotine concentrations were slightly higher under conditions of alkaline compared with acidic urine (Figure 2). From the areas under the curves in Figure 2, the increases in plasma nicotine which occurred with the alkaline versus acidic urine condition were 66%, 35% and 30% respectively for the 2 mg gum, 4 mg gum and cigarettes.

The effect of urine pH on nicotine excretion is shown in Figure 3. Under acidic control 18 to 30 times more nicotine appeared in the urine than under alkaline conditions. Total nicotine excretion over 8 h was 1,024, 1,072 and 1,308 µg for the 2 mg, 4 mg gums and cigarette smoking respectively under acidic conditions; compared to 33.7, 59.2 and 43.6 µg under alkaline conditions.

The urinary nicotine excretion, under conditions of controlled acidity, was related to urine flow and was higher at midday (between 11 and 13 h) when urine flow was maximal (Figure 4).

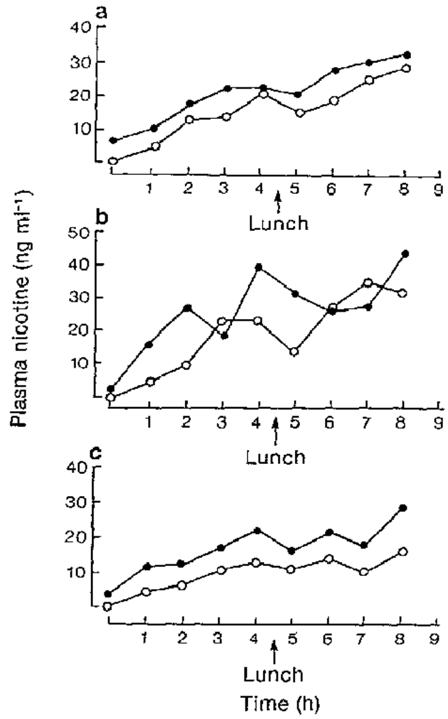


Figure 2 Plasma nicotine levels immediately before (a) smoking one cigarette, (b) chewing a 4 mg and (c) 2 mg nicotine gum every hour for 8 h. O acidic controlled urinary pH (4.7–5.3); ● alkaline controlled urinary pH (7.4–8.0). The differences between acidic and alkaline conditions when smoking cigarettes and taking 2 mg nicotine gum are highly significant (t = 6.1 and 7.1 respectively, d.f. 8, $P < 0.00$) but only just significant on a one-tailed test when taking 4 mg nicotine gum ($t = 2.1$, d.f. 8, $P < 0.05$).

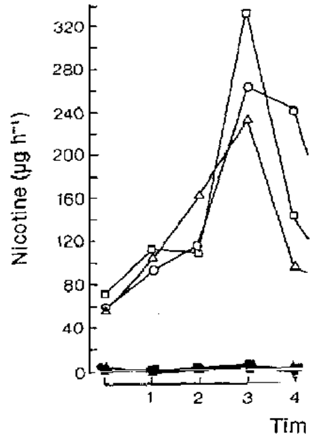


Figure 3 Urinary excretion smoking a cigarette (O, ●) chewi 4 mg (□, ■) nicotine gum every symbols acidic controlled urin Closed symbols alkaline con (7.4–8.0).

Discussion

The data suggest that accumulati in plasma when taking nicotine gum. Although absorption was

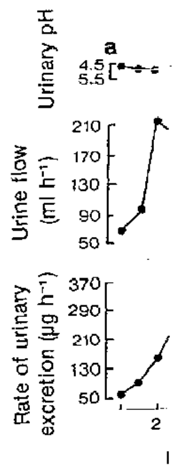
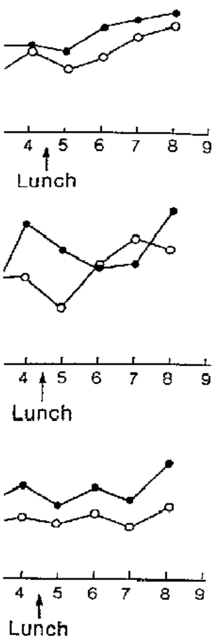


Figure 4 Relation of urinary pH when (a) chewing 2 mg ni hour for 8 h.



levels immediately before
›) chewing a 4 mg and (c)
hour for 8 h. O acidic
5.3); ● alkaline controlled
ifferences between acidic
n smoking cigarettes and
re highly significant (t =
.f. 8, P < 0.00) but only
ed test when taking 4 mg
P < 0.05).

ne versus acidic urine
ind 30% respectively for
! cigarettes.
on nicotine excretion is
dic control 18 to 30 times
ı the urine than under
cotine excretion over 8 h
3 µg for the 2 mg, 4 mg
respectively under acidic
/, 59.2 and 43.6 µg under

tion, under conditions of
ed to urine flow and was
11 and 13 h) when urine

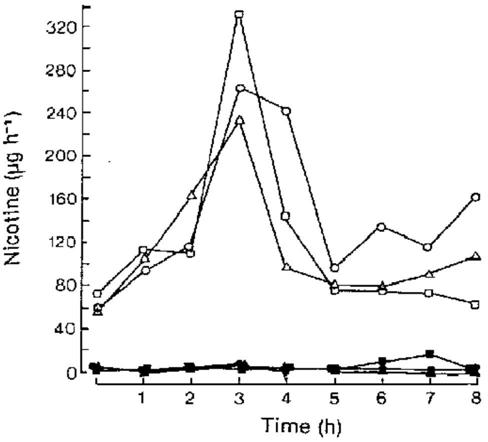


Figure 3 Urinary excretion of nicotine when smoking a cigarette (O, ●) chewing a 2 mg (△, ▲) and 4 mg (□, ■) nicotine gum every hour for 8 h. Open symbols acidic controlled urinary pH (4.7–5.3); Closed symbols alkaline controlled urinary pH (7.4–8.0).

Discussion

The data suggest that accumulation of nicotine occurs in plasma when taking nicotine containing chewing-gum. Although absorption was slower, plasma levels comparable to cigarette smoking were built up on 4 mg (but not 2 mg) nicotine gum. With hourly nicotine dosage, plasma concentrations produced by 4 mg nicotine by gum were 91% of those produced by 1.3 mg nicotine via deeply inhaled cigarette smoke. It is not known how much the pharmacological rewards of inhaled cigarette smoking are due to some effect of the rapid plasma nicotine peaks or to the maintenance of a certain trough level. This probably depends on the type of smoker. The data from this study suggest that nicotine chewing-gum is more suited to trough maintenance or to providing whatever pharmacological effects are produced by the slower buccal absorption of nicotine as in the case of non-inhaled cigar smoking. The rate of nicotine absorption from the gum is limited partly by the rate of buccal absorption but also by the rate of it release from the gum:- 18%, 36%, 61% and 91% respectively after 2, 5, 10 and 20 min chewing (Fernö *et al.*, 1973).

The urinary excretion of nicotine was influenced markedly by pH and the rate of urine flow. The influence of urinary pH is in keeping with previous studies (Beckett *et al.* 1965; Beckett & Triggs, 1966; Haag & Larson, 1942). However, the very clear relation of the rate of urinary nicotine excretion to urinary flow, under acidic conditions, is not generally accepted and is in fact contrary to the conclusions of Beckett and his colleagues (1971a, 1971b, 1972). In his earlier work Beckett also found that the amount of nicotine excreted in urine was influenced by the rate of urine flow (Beckett & Triggs, 1966). However, in subsequent publications (Beckett *et al.*, 1971a, 1971b,

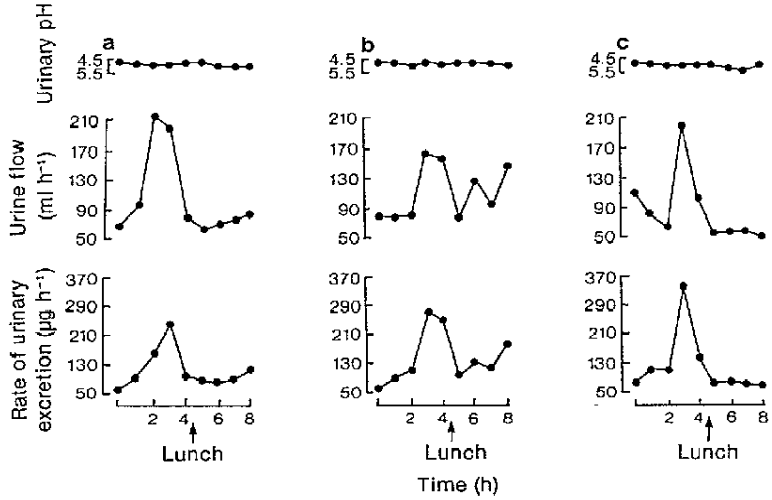


Figure 4 Relation of urinary nicotine excretion to urine flow rate under conditions of controlled acidic urinary pH when (a) chewing 2 mg nicotine gum, (b) smoking one cigarette and (c) chewing 4 mg nicotine gum every hour for 8 h.

PM3006723483

1972) he and his colleagues came to different conclusions reporting, for example, that 'when the urine is adjusted to an acid pH the excretion of cotinine but not of nicotine is affected by changes in urine output' (Beckett *et al.*, 1971b). In another report, they mentioned 'the volume dependent excretion of cotinine but not nicotine' (Beckett *et al.*, 1972). A possible reason for this apparent discrepancy may be that the experiments in which they failed to find a urine-flow effect involved a single relatively small dose of nicotine given to subjects who had not smoked for as long as 36 h. Under these conditions, apart from the first hour, the nicotine excretion rate was usually below 1.0 µg/min. It is possible that at such low levels their measurement of nicotine may have been insufficiently sensitive to detect the influence of urine flow rate superimposed on the decline curve following a single small dose of nicotine in nicotine-depleted subjects.

Despite the fairly large (18–30 fold) variation in urinary nicotine excretion produced by changes in pH and urine flow, the effect on plasma nicotine concentrations was relatively small. Indeed the plasma levels did not seem to be noticeably affected (Figure 2) when the urine flow and nicotine excretion rate were maximal at 2 to 4 h after the start of each experiment (Figures 3 & 4). On the other hand, plasma concentrations were 30%–66% higher under conditions of alkaline compared with acidic urine. The fact that plasma nicotine levels were affected by the pH but not by the rate of urine flow suggests that the effect of pH on the plasma levels may have been mediated less by the influence on urinary nicotine excretion rate than by some other mechanism such as an influence on nicotine absorption or one of the nicotine recycling processes (Russell, 1976). The effect of pH on plasma nicotine concentrations helps to explain the findings of Schachter, Kozlowski & Silverstein (1977) who showed that cigarette smokers could be made to modify their cigarette consumption by manipulating their urinary pH.

Compared with the doses of nicotine administered over the 8 h experimental periods (10.4, 16.0 and 32 mg respectively for cigarettes, 2 mg and 4 mg gum) the amounts excreted in the urine were trivial even under acidic conditions (1.3, 1.0 and 1.1 mg, or 12.5%, 6.3% and 3.4% respectively for cigarettes, 2 mg and 4 mg gum). This may explain why major changes in urinuary excretion of nicotine had a relatively small effect on the plasma levels. Despite the marked reduction in urinary excretion under the alkaline conditions, excessive accumulation of nicotine did not occur. These findings suggest that in this subject the plasma nicotine was influenced more by the rate of metabolism than by the rate of excretion of unchanged nicotine in the urine. The tendency for plasma nicotine to fall just after lunch (Figure 2) cannot be explained by an increase in nicotine excretion, for this was maximal 1–2 h before lunch (Figure 4). It could, however, be explained by an increase in the rate of metabolism of nicotine brought on by the postprandial increase in blood flow to the gut and hence the liver (Henry & Meehan, 1971).

On the basis of the afternoon plasma nicotine concentration when taking the 2 mg nicotine chewing-gum, the subject in this study was not markedly atypical compared to a sample of 15 smokers attending a withdrawal clinic; they averaged 10.9 ng/ml and ranged from 5.4 to 21.8 ng/ml under conditions of fluctuating urinary pH (Russell *et al.*, 1976).

Implications from data based on a single subject obviously require replication with more subjects. Nevertheless, these findings do suggest that (1) 4 mg nicotine chewing-gum has some potential as a pharmacological substitute for smoking; (2) Notwithstanding Beckett and his colleagues previous work (1971a, 1971b, 1972), urinary flow influences the nicotine excretion rate under acidic conditions; (3) Fluctuations in urinary nicotine excretion have a relatively small effect on plasma nicotine concentration; (4) The higher plasma nicotine concentration when taking sodium bicarbonate as opposed to ammonium chloride may be mediated more by an influence on nicotine absorption or one of the nicotine recycling processes than by changes in urinary excretion of nicotine; (5) There may be a tendency for the plasma nicotine concentration to decrease more rapidly after lunch which could contribute to an increased urge to smoke at this time.

We thank A.B. Leo and Co., Helsingborg, Sweden for supplying the nicotine chewing-gum; Peter Rutledge, our willing subject; the Medical Research Council and Department of Health and Social Security for financial support; and Jean Crutch for secretarial help. Reprint requests should be addressed to M.A.H.R.

References

ARMITAGE, A.K., DOLLERY, C.T., GEORGE, C.F., HOUSEMAN, T.H., LEWIS, P.J. & TURNER, D.M. (1975). Absorption and metabolism of nicotine from cigarettes. *Br. med. J.*, **4**, 313–316.

BECKETT, A.H., GORROD, J.W. & JENNER, P. (1971a). The analysis of nicotine-l'-N-oxide in urine in the presence of nicotine and cotinine and its application to the study of *in vivo* nicotine metabolism in man. *J. Pharm. Pharmac.*, **23**, Suppl. 55S–61S.

BECKETT, A.H., GORROD, J.W. & JENNER, P. (1971b). The effect of smoking on nicotine metabolism *in vivo* in man. *J. Pharm. Pharmac.*, **23**, Suppl. 62S–67S.

BECKETT, A.H., GORROD, J.W. & JE
possible relation between pKa, anc
the amounts excreted in urine of so
given to man. *J. Pharm. Pharmac.*, 2

BECKETT, A.H., ROWLAND, M. & T
Significance of smoking in inves
excretion rates of amines in man. *Na*

BECKETT, A.H. & TRIGGS, E.J. (196
nicotine and its metabolite, cotini
chromatography. *Nature*, **211**, 1415

FERNÖ, O., LICHTNECKERT, S.J.A. &
(1973). A substitute for tobacco
pharmacologia, **31**, 201–204.

FEYERABEND, C., LEVITT, T. & RUSS
A rapid gas-liquid chromatogra
nicotine in biological fluids. *J. Ph*
434–436.

HAAG, H.B. & LARSON, P.S. (1942).
nicotine in the body. 1. The effect
excretion of nicotine by tobacco s
exp. Ther., **76**, 235–239.

:ion of nicotine had a
plasma levels. Despite the
ry excretion under the
accumulation of nicotine
ngs suggest that in this
was influenced more by
y the rate of excretion of
urine. The tendency for
after lunch (Figure 2)
n increase in nicotine
nal 1–2 h before lunch
r, be explained by an
lism of nicotine brought
ise in blood flow to the
& Meehan, 1971).
on plasma nicotine con-
2 mg nicotine chewing-
udy was not markedly
ample of 15 smokers
linic; they averaged
5.4 to 21.8 ng/ml under
ary pH (Russell *et al.*,

:ed on a single subject
with more subjects.
) suggest that (1) 4 mg
some potential as a
for smoking; (2)
his colleagues previous
nary flow influences the
acidic conditions; (3)
tine excretion have a
na nicotine concentra-
nicotine concentration
onate as opposed to
mediated more by an
ı or one of the nicotine
changes in urinary
may be a tendency for
:ion to decrease more
uld contribute to an
ime.

Helsingborg, Sweden for
m; Peter Rutledge, our
Research Council and
l Security for financial
ecretarial help. Reprint
A.H.R.

plication to the study of
an. *J. Pharm. Pharmac.*,

ENNER, P. (1971b). The
tabolism *in vivo* in man.
2S–67S.

BECKETT, A.H., GORROD, J.W. & JENNER, P. (1972). A possible relation between pKa, and lipid solubility and the amounts excreted in urine of some tobacco alkaloids given to man. *J. Pharm. Pharmac.*, **24**, 115–120.

BECKETT, A.H., ROWLAND, M. & TRIGGS, E.J. (1965). Significance of smoking in investigations of urinary excretion rates of amines in man. *Nature*, **207**, 200–201.

BECKETT, A.H. & TRIGGS, E.J. (1966). Determination of nicotine and its metabolite, cotinine, in urine by gas chromatography. *Nature*, **211**, 1415–1417.

FERNÖ, O., LICHTNECKERT, S.J.A. & LUNDGREN, C.E.G. (1973). A substitute for tobacco smoking. *Psychopharmacologia*, **31**, 201–204.

FEYERABEND, C., LEVITT, T. & RUSSELL, M.A.H. (1975). A rapid gas-liquid chromatographic estimation of nicotine in biological fluids. *J. Pharm. Pharmac.*, **27**, 434–436.

HAAG, H.B. & LARSON, P.S. (1942). Studies on the fate of nicotine in the body. I. The effect of pH on the urinary excretion of nicotine by tobacco smokers. *J. Pharmac. exp. Ther.*, **76**, 235–239.

HENRY, J.P. & MEEHAN, J.P. (1971). In *The Circulation*, p. 154. Chicago: Yearbook Medical Publishers Inc.

HERXHEIMER, A., GRIFFITHS, R.L. HAMILTON, B. & WAKEFIELD, M. (1967). Circulatory effects of nicotine aerosol inhalations and cigarette smoking in man. *Lancet*, **ii**, 754–755.

RUSSELL, M.A.H. (1976). Tobacco smoking and nicotine dependence. In *Research Advances in Alcohol and Drug Problems*, ed Gibbins, R.J. 3, 1–47. New York: Wiley & Sons.

RUSSELL, M.A.H., FEYERABEND, C. & COLE, P.V. (1976). Plasma nicotine levels after cigarette smoking and chewing nicotine gum. *Br. med. J.*, **1**, 1043–1046.

SCHACHTER, S., KOZLOWSKI, L.T. & SILVERSTEIN, B. (1977). Effects of urinary pH on cigarette smoking. *J. exp. Psychol: General*, **106**, 3–40.

(Received June 14, 1977)